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09/030,571	02/24/1998	CHARLES R. CANTOR	25491-2401G	7542

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EXAMINER

FORMAN, BETTY J

ART UNIT PAPER NUMBER

1634

DATE MAILED: 02/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/030,571

Applicant(s)

CANTOR ET AL.

Examiner

BJ Forman

Art Unit

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 25 November 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 70,72-79,92-94,123,124,127-133 and 135-138 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 70,72-79,92-94,123,124,127-133 and 135-138 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 25 November 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>8/03</u> . | 6) <input type="checkbox"/> Other: _____ |

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FINAL ACTION

Status of the Claims

1. This action is in response to papers filed 25 November 2003 in which claims 70, 74, 75, 123, 124, 127, 128, 135 were amended, claim 134 was canceled and claims 136-138 were added and further in view of the Supplemental Information Disclosure Statement filed 13 August 2003. All of the amendments have been thoroughly reviewed and entered.

The previous rejections in the Office Action dated 27 May 2003, not reiterated below are withdrawn in view of the amendments and new grounds for rejection. All of the arguments have been thoroughly reviewed and are discussed below as they apply to the instant rejections. New grounds for rejection necessitated by the amendments and Supplemental Information Disclosure Statement are discussed.

Claims 70, 72-79, 92-94, 123-124, 127-133, 135-138 are under prosecution.

Specification

2. Applicant's amendments to the specification, pages 46-47 are acknowledged. The amendments have been entered.

Drawings

3. The amended drawings received on 25 November 2003 are acknowledged. These drawings are accepted by the examiner.

Information Disclosure Statement

4. The references listed on the 1449 received 13 August 2003 are acknowledged. The reference lined through has not been considered because the reference is a non-English language document.

Claim Rejections - 35 USC § 112

35 U.S.C. 112: First paragraph

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 70, 72-79, 92-94, 123-124, 127-133, 135-138 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

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a. The recitation “wherein the variable sequence is not at the terminus” is added to the newly amended independent claim 70 (from which Claims 72, 73, 77-79 depend). However, the specification fails to define or provide any disclosure to support such claim recitation.

Applicant points to page 20, lines 14-17 and page 27, lines 6-25 for support for the newly added limitation. However, the cited passages merely teaches: “a terminal single-stranded portion of length S, and a random nucleotide sequence within the single-stranded portion”. Nowhere in the cited passages does the specification teach the variable sequence is not at the terminus. Hence, the amendments discussed above constitute new matter.

Any negative limitation or exclusionary proviso must have basis in the original disclosure. If alternative elements are positively recited in the specification, they may be explicitly excluded in the claims. See *In re Johnson*, 558 F.2d 1008, 1019, 194 USPQ 187, 196 (CCPA 1977) (“[the] specification, having described the whole, necessarily described the part remaining.”). See also *Ex parte Grasselli*, 231 USPQ 393 (Bd. App. 1983), *aff’d mem.*, 738 F.2d 453 (Fed. Cir. 1984). The mere absence of a positive recitation is not basis for an exclusion. Any claim containing a negative limitation which does not have basis in the original disclosure should be rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement (see MPEP 2173.05(i))

b. The recitation “a variable terminal nucleotide sequence of between about 3-10 nucleotides in length” is added to the newly amended independent claim 74 (from which Claims 75, 76, 92-94, 123, 124, 136 depend). However, the specification fails to define or provide any disclosure to support such claim recitation.

Applicant points to page 26, lines 14-28 and page 21, lines 1-8 for support for the instant amendment. However, nowhere in the cited passages is there a teaching of the claimed variable terminal sequence having a length of 3-10 nucleotides as newly claimed. Hence, the amendment constitutes new matter.

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c. The recitations “each probe comprises a predetermined sequence of fixed and non-fixed positions”; the array is divided into subarrays”; “for each subarray a selected base of the...occupies the fixed positions”; “the fixed positions of the different subarrays are occupied by a different selected base” is added to the newly amended independent claim 127 (from which claims 128-133, 135, 137, 138 depend). Applicant points to the teaching of Macevics WO 90/04652 (incorporated by reference) to support the amendments to the instant claim. However, Macevics merely teaches subsets of probes wherein positions within the probe contains every possible base. Macevics does not teach “each probe comprises a predetermined sequence of fixed and non-fixed positions”, but instead teaches general methods for designing probe sets. Macevics does not teach “array is divided into subarrays” but instead teaching probe mixtures. Macevics does not teach “for each subarray a selected base of the...occupies the fixed positions” but instead teaches four subsets containing every possible sequence. Macevics does not teach “the fixed positions of the different subarrays are occupied by a different selected base” but instead teaches general methods for designing probe sets (Column 2, lines 55-Column 3, lines 35). Applicant appears to be extrapolating from Macevics terminology and structure not clearly defined by the reference. Hence, the amendments constitute new matter.

MPEP 2163.06 notes “IF NEW MATTER IS ADDED TO THE CLAIMS, THE EXAMINER SHOULD REJECT THE CLAIMS UNDER 35 U.S.C. 112, FIRST PARAGRAPH - WRITTEN DESCRIPTION REQUIREMENT. *IN RE RASMUSSEN*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981).” MPEP 2163.02 teaches that “Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application.” MPEP 2163.06 further notes “WHEN AN AMENDMENT IS FILED IN REPLY TO AN OBJECTION OR REJECTION BASED ON 35 U.S.C. 112, FIRST PARAGRAPH, A STUDY OF THE ENTIRE APPLICATION IS OFTEN NECESSARY TO DETERMINE WHETHER OR NOT “NEW MATTER” IS INVOLVED. *APPLICANT SHOULD THEREFORE SPECIFICALLY POINT OUT THE SUPPORT FOR ANY AMENDMENTS MADE TO THE DISCLOSURE*” (emphasis added).

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35 U.S.C. 112: Second paragraph

7. Claims 75, 136 and 137 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 75 is indefinite for the recitation "which is fixed to a solid support because it is unclear whether the recitation is intended to limit the nucleic acid probes or array of Claim 74. It is suggested that the claim be amended to clarify.

Claim 136 is indefinite for the recitation "the constant portion" because the recitation lacks proper antecedent basis in Claim 74. It is suggested that the claim be amended to provide proper antecedent basis.

Claim 137 is indefinite for the recitation "which is fixed to a solid support because it is unclear whether the recitation is intended to limit the nucleic acid probes or array of Claim 127. It is suggested that the claim be amended to clarify.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

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(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. Claims 70, 72, 74, 76-79, 92-94, 124, 127, 129-131, 133, 135-137 are rejected under 35 U.S.C. 102(e) as being anticipated by Deugau et al (U.S. Patent No. 5,508,169, filed 6 April 1990).

The claims have been amended to introduce numerous method steps for making the array of probes e.g. hybridizing, ligating, predetermined, divided, selected. However, the courts have stated that patentability of a product is based on the product, not the method of making the product. The claims are interpreted based on the resulting product as discussed below.

Regarding Claim 70, Deugau et al disclose an array of nucleic acid probes (i.e. complete panel of indexing linkers) wherein each probe has a double-stranded portion and a terminal single stranded portion comprising a variable nucleotide sequence within the single-stranded portion (Column 11, lines 14-25, Fig. 2 and Claim 33). Furthermore, Deugau et al teach the single-stranded portion varies in length (Columns 15-16, Table I and Table II). The instant specification (page 30, line 10) defines variable as varying in length. Therefore, Deugau et al teach a variable sequence as claimed. Additionally, because the single stranded portion of Deugau et al have a terminal nucleotide and the number of nucleotides between the terminal nucleotide and the double stranded portion of the probe varies, the variable single stranded sequence would be interpreted as being not at the terminus, but instead between the terminus and the double stranded portion. Hence, Deugau et al teach the probes as claimed.

The courts have stated that claims must be given their broadest reasonable interpretation consistent with the specification *In re Morris*, 127 F.3d 1048, 1054-55,

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44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997); *In re Prater*, 415 F.2d 1393, 1404-05, 162 USPQ 541, 550-551 (CCPA 1969); and *In re Zletz*, 893 F.2d 319, 321-22, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989) (see MPEP 2111).

Regarding Claim 72, Deugau et al disclose the array wherein the double-stranded portion (i.e. common sequence # 1026, # 1504 and # 1701) is between about 3-20 nucleotide and the single stranded portion is between about 3-20 nucleotides (Columns 15-16, Table I and Table II).

Regarding Claim 74, Deugau et al teach an array of probes comprising a first nucleic acid hybridized to the second nucleic acid forming a hybrid having a double-stranded portion and a single-stranded portion (Column 11, lines 14-25; Columns 15-16, Table I and Table II; Fig. 2; and Claim 33). The courts have stated that patentability of a product is based on the product, not method of making the product. Because Deugau et al teach the product i.e. array of probes, the disclose the instantly claimed array.

“[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is **based on the product itself**. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process.” *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) see MPEP 2113.

Regarding Claim 76, Deugau et al teach the array wherein the solid support is a two-dimensional matrix with multiple probe binding sites i.e. the probes are attached to spatially segregated solid phase substrates (Column 10, lines 45-51).

Regarding Claim 77, Deugau et al teach the array wherein the probes are labeled with a detectable label (Claim 27).

Regarding Claim 78, Deugau et al teach the array wherein the label comprises a radioisotope or fluorescent chemical (Claims 27 & 28).

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Regarding Claim 79, Deugau et al teach the array wherein the nucleic acids are DNA (Claims 25 and 33).

Regarding Claim 92, Deugau et al teach the array wherein the probes are labeled with a detectable label (Claim 27).

Regarding Claim 93, Deugau et al teach the array wherein the label comprises a radioisotope or fluorescent chemical (Claims 27 & 28).

Regarding Claim 94, Deugau et al teach the array wherein the nucleic acids are DNA (Claims 25 and 33).

Regarding Claim 124, Deugau et al teach the array comprising about 4ⁿ different nucleic acid probes (i.e. complete panel of indexing linkers) (Column 11, lines 14-25).

Regarding Claim 127, Deugau et al disclose an array of nucleic acid probes (i.e. complete panel of indexing linkers) wherein each probe has a double-stranded portion and a terminal single stranded portion comprising a variable nucleotide sequence within the single-stranded portion (Column 11, lines 14-25, Fig. 2 and Claim 33). Furthermore, Deugau et al teach the single-stranded portion varies in length (Columns 15-16, Table I and Table II). Deugau et al teach their single-stranded portions are selected from all possible permutations and combinations of A, C, G, T (Column 9, lines 16-27). The single-stranded portions of Deugau et al inherently have one base at fixed positions and unfixed positions and the other bases would be in the remaining positions. The claim appears to be reciting method steps of dividing the probes and/or designing the probes and/or mental steps for defining or designing the single-stranded portions of the probe. However, the claim is drawn to a product i.e. array comprising nucleic acid probes with single and double-stranded portions. The courts have stated that "even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though

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the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) see MPEP 2113.

Regarding Claim 129, Deugau et al teach the array wherein the probes are labeled with a detectable label (Claim 27).

Regarding Claim 130, Deugau et al teach the array wherein the label comprises a radioisotope or fluorescent chemical (Claims 27 & 28).

Regarding Claim 131, Deugau et al teach the array wherein the nucleic acids are DNA (Claims 25 and 33).

Regarding Claim 133, Deugau et al teach the support is two dimensional i.e. an array wherein each member of the array is attached to spatially separate part of a support (Column 11, lines 23-25).

Regarding Claim 135, Deugau et al teach the array wherein the probe comprises a nucleic acid analog i.e. labeled with a reporter group (Column 11, lines 17-20).

Regarding Claim 136, Deugau et al teach the array wherein the constant portion includes an enzyme restriction site (Column 6, lines 1-21).

Regarding Claim 137, Deugau et al teach the array wherein the probes are immobilized to a solid support (Column 11, lines 14-25)

Response to Arguments

10. Applicant states that Deugau et al does not teach an array of probes comprising a variable sequence not at the terminus. The argument has been considered but is not found persuasive. As stated above, Deugau et al teach the single-stranded portion varies in length (Columns 15-16, Table I and Table II). The instant specification (page 30, line 10) defines variable as varying in length. Therefore, Deugau et al teach a variable sequence as claimed. Additionally, because the single stranded portion of Deugau et al have a terminal nucleotide and the number of nucleotides between the terminal nucleotide and the double stranded portion of the probe varies, the variable single stranded sequence would be interpreted as being

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not at the terminus, but instead between the terminus and the double stranded portion.

Hence, Deugau et al teach the probes as claimed.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

12. Claim 73, 123, 128 and 138 are rejected under 35 U.S.C. 103(a) as being unpatentable over Deugau et al (U.S. Patent No. 5,508,169, filed 6 April 1990) in view of Brenner et al (Proc. Natl. Acad. Sci. USA, 1989, 86: 88902-8906).

Regarding Claims 73, 123, 128 and 138, Deugau et al disclose the array of nucleic acid probes (i.e. complete panel of indexing linkers) wherein each probe has a double-stranded portion at the 3' terminus, a single stranded portion at the 5' terminus and a random nucleotide sequence of length R within the single-stranded portion (Column 11, lines 14-25, Fig. 2 and Claim 33) wherein the probes are immobilized to a solid support (Column 11, lines 14-25) but they do not specifically teach the means by which the probes are immobilized. However, coupling agents e.g. biotin/streptavidin immobilization was well known in the art at the time the claimed invention was made as taught by Brenner et al who teach that biotin/streptavidin provides a versatile means of capture immobilization (page 8904, second full paragraph). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the biotin/streptavidin of Brenner et al to the

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immobilization of Deugau et al based on the teaching of Brenner et al to thereby provide versatile capture immobilization (page 8904, second full paragraph).

Response to Arguments

13. Applicant states that Deugau et al does not teach an array of probes comprising a variable sequence not at the terminus. The argument has been considered but is not found persuasive. As stated above, Deugau et al teach the single-stranded portion varies in length (Columns 15-16, Table I and Table II). The instant specification (page 30, line 10) defines variable as varying in length. Therefore, Deugau et al teach a variable sequence as claimed. Additionally, because the single stranded portion of Deugau et al have a terminal nucleotide and the number of nucleotides between the terminal nucleotide and the double stranded portion of the probe varies, the variable single stranded sequence would be interpreted as being not at the terminus, but instead between the terminus and the double stranded portion. Hence, Deugau et al teach the probes as claimed.

14. Claims 75 and 132 are rejected under 35 U.S.C. 103(a) as being unpatentable over Deugau et al (U.S. Patent No. 5,508,169, filed 6 April 1990) in view of Ghosh et al (Nucleic Acids Research, 1987, 15: 5353-5372).

Regarding Claims 75 and 132, Deugau et al teach an array of probes comprising a first nucleic acid hybridized to the second nucleic acid forming a hybrid having a double-stranded portion and a single-stranded portion (Column 11, lines 14-25; Columns 15-16, Table I and Table II; Fig. 2; and Claim 33). wherein the probes are fixed to a solid support as taught by Ghosh et al (Column 10, lines 45-51 and Claim 26) but they do not specifically teach the

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material from which the solid support is made. However, Ghosh et al teach their solid support is selected from plastics and resins (page 5356, first full paragraph-page 5357, last paragraph).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the solid supports of Ghosh et al to the immobilization of Deugau et al and to immobilize the probes onto plastic or resin support based on the suggestion of Deugau et al (Column 10, lines 45-51 and Claim 26) thereby utilizing well known supports for the expected benefits of successful immobilization.

15. Applicant's amendment and Supplemental Information Disclosure Statement necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

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Conclusion

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (571) 272-0741 until 13 January 2004. The examiner can normally be reached on 6:00 TO 3:30 Monday through Thursday and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (703) 308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 308-8724 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-0507.



BJ Forman, Ph.D.
Primary Examiner
Art Unit: 1634
February 12, 2004